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Sleep Quality and Nocturnal Symptoms in a Community-Based COPD Cohort

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ABSTRACT

Small studies have suggested that patients with chronic obstructive pulmonary disease (COPD) have poor sleep quality. Our aim was to examine the prevalence of subjective sleep-related complaints and predictors of poor sleep quality in a large community-based COPD cohort. We analyzed cross-sectional data on sleep questionnaire responses from the Canadian Cohort of Obstructive Lung Disease (CanCOLD) study, a population-based, prospective longitudinal cohort study across Canada. The cohort comprises a COPD group and two matched non-COPD (never-smokers and ever-smokers) groups. Sleep-related symptoms were assessed using questionnaires including Pittsburgh Sleep Quality Index (PSQI). A total score of PSQI $>$ 5 is indicative of poor sleep quality. Health-related quality of life measures and the presence of mood disturbance were assessed using Short Form-36™ Health Survey (SF-36) multi-item questionnaires and Hospital Anxiety and Depression Scale (HADS), respectively. Predictors of poor sleep quality were analyzed using multivariable logistic regression analysis. Of the 1123 subjects, 263 were healthy controls, 323 at-risk controls, and 537 had COPD (297 had mild, 240 with moderate to severe disease). The mean PSQI score was not significantly different between groups. COPD patients with poor sleep quality had lower diffusion capacity, higher HADS anxiety and depression scores and lower SF-36 mental and physical component summary scores than COPD patients classified as good sleepers. The presence of restless legs and obstructive sleep apnea symptoms, waist circumference, predicted diffusion capacity and HADS anxiety and depression scores were identified as independent predictors of poor sleep quality.

List of abbreviations: ATS: American Thoracic Society; BA: beta-agonist; BOLD: Burden of Obstructive Lung Disease; CanCOLD: Canadian Cohort of Obstructive Lung disease; COPD: chronic obstructive pulmonary disease; DLCO: diffusion capacity; DSQoL: disease-specific quality of life; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HADS: Hospital Anxiety and Depression Scale; HRQoL: health-related quality of life; ICS: inhaled corticosteroids; MA: muscarinic antagonist; MCS: mental component summary score; OSA: obstructive sleep apnea; PCS: physical component summary score; PSQI: Pittsburgh Sleep Quality Index; QoL: quality of life (QoL); REM: rapid eye movements; SF-36: Short Form-36™ Health Survey

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Introduction

Chronic obstructive pulmonary disease (COPD) affects approximately 10% of adults aged ≥40 years and is the fourth leading cause of mortality worldwide [1, 2]. It is estimated that more than 60% of patients with COPD experience sleep-related symptoms [3, 4]. These sleep-related complaints include insomnia, non-restorative sleep and daytime fatigue [3]. Studies that examined polysomnography variables have described reduced sleep time, reduced REM sleep, frequent sleep stage shifts and micro-arousals in COPD patients [5, 6]. Poor sleep quality in COPD patients has been reported in various studies with prevalence ranging from 40% to 75% of COPD patients [7, 8].

The causes of poor sleep quality in COPD are poorly understood, although a bidirectional association between poor sleep and COPD severity score has been suggested, i.e. COPD symptoms such as cough and dyspnea may be responsible for poor sleep quality. Alternatively, disturbed sleep can contribute to poor COPD-related outcomes [9]. A number of other factors likely interplay. First, Chang et al. identified that nocturnal symptoms such as wheezing, phlegm production and inhaled corticosteroid may disturb sleep [10]. Moreover, systemic steroids have well-known side effects including insomnia. Second, nocturnal hypoventilation and; ventilation/perfusion abnormalities are possible mechanisms that can accentuate nocturnal hypoxemia in

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COPD patients, particularly during REM sleep, and can worsen sleep quality. Third, obstructive sleep apnea (OSA) is a common co-morbidity in COPD patients. COPD and OSA coexist in at least 1% of COPD patients. Indeed, OSA has been highlighted as one of the under-recognized co-morbidity in COPD in recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [11]. Coexistence of OSA and COPD can exacerbate poor sleep quality and is associated with increased risk of COPD exacerbation, pulmonary hypertension and cardiovascular disease-related mortality than COPD alone [12]. Finally, compromised respiratory mechanics due to hyperinflation, airflow obstruction and respiratory muscle insufficiency can add to work of breathing and elicit arousals [12]. Irrespective of the etiology, existing literature suggests that sleep disturbance in patients with COPD can lead to poor outcomes including increased risk of COPD exacerbations [13], neurocognitive dysfunction [9] and poor functional exercise capacity [14].

The literature that explores the relationship between sleep and COPD has many limitations. For instance, the correlation between sleep impairment and its adverse effect on quality of life (QoL) in COPD patients has only been derived from small studies, usually from specialized respiratory clinics or hospitalized patients. Large-scale population-based studies evaluating the epidemiology of sleep quality and disturbance are needed to validate the results of small studies and to raise awareness of the clinical implications of sleep quality in COPD. We sought to test the overall hypothesis that diverse problems with sleep are highly prevalent in COPD patients, and that sleep impairment and sleep-related symptoms have an important impact on QoL. The primary objective of this study was to examine the prevalence of subjective sleep-related complaints including insomnia, OSA and restless legs syndrome in a large community-based COPD cohort. As a secondary objective, we aimed to describe the relationships between sleep quality and potential risk factors for poor sleep such as severity of airflow obstruction, and to determine if sleep quality was associated with QoL including health-related quality of life (HRQoL) and disease-specific quality of life (DSQoL) indices.

Methods

Study population

We used data from the population-based, prospective Canadian Cohort of Obstructive Lung Disease (CanCOLD) study. The details of the CanCOLD study design and protocol have been previously published [2]. Briefly, subjects in this cohort were recruited from nine study sites in Canada: Calgary, Halifax, Kingston, Montreal, Ottawa, Quebec, Saskatoon, Toronto and Vancouver between August 2005 and May 2009. The study was initiated in Vancouver as part of the Burden of Obstructive Lung Disease (BOLD) study and was subsequently completed at other eight sites [15]. Random sample at each site was drawn from a well-defined area with total population of at least 250,000 people. Non-institutionalized adults aged $\geq$ 40 years were included. Informed consent was obtained from all participants and respective institutional ethical review boards approved study. At the baseline visit, demographic information, spirometry and medical history were collected. Measurements were obtained in five domains including study questionnaire, pulmonary function assessment, CT scan of the chest, blood test and health administrative databases [2].

Spirometric measurements

Spirometry, lung volumes and DLCO were obtained in accordance with 1986 American Thoracic Society standards [16]. Certified technicians used EasyOne^{TM} spirometer (ndd Medical Technologies, Andover, MA, USA) to collect lung function data. Pre- and post-bronchodilator spirometry variables were measured before and 15 min after 200 µg of salbutamol, respectively. All spirograms were reviewed and graded according to acceptability and reproducibility criteria from the ATS and European Respiratory Society criteria [15, 17].

Ascertainment of COPD diagnosis and severity

The cohort is comprised of two COPD groups (mild COPD and moderate to severe COPD) and two age- and sex-matched non-COPD groups (healthy control and at-risk individuals). Chronic airflow obstruction (COPD) in this study was defined based on the presence of post-bronchodilator FEV_1/FVC ratio <0.70 as defined by GOLD. Severity of COPD was categorized according to GOLD stages of severity classification as mild or GOLD1 ($FEV_1 \geq 80\%$ predicted) and moderate-severe or GOLD2+ ($FEV_1 \leq 80\%$ predicted) [18]. Non-COPD subgroups included healthy and at-risk participants. Healthy individuals were never-smokers with normal post-bronchodilator spirometry. At-risk individuals were ever-smokers and normal post-bronchodilator spirometry [2]. Ever-smokers were individuals who had a positive lifetime history of 400 cigarettes or 1 cigarette per day for 1 year [19].

Sleep quality and patient characteristics

In order to assess perceived health-related QoL and health status, Short Form-36^{TM} Health Survey (SF-36) multi-item questionnaire was utilized. SF-36 provides an assessment of an overall functional health and well-being from patient's perspective. This questionnaire measures eight health domains including physical functioning, role limitations due to physical health, bodily pain, general mental health, role limitations due to emotional problems, vitality, social functioning and general health perceptions. These eight scales are aggregated into two summary measures: physical component summary score (PCS) and mental component summary score (MCS). Physical component covers limitations in daily life due to health problems, whereas mental component addresses psychological stress. Global SF-36 scores range from 0 to 100, with higher scores indicating better health on each dimension. For each domain (physical and mental

composite), mean score is up to 50. The exact balance between the physical and the mental components and their contributions to the health-related QoL probably is not well known [20].

Hospital Anxiety and Depression Scale (HADS) was used to determine the presence of depression and anxiety among individuals in CanCOLD cohort. It consists of 14 total items, 7 items each for depression and anxiety scale. A score between 0 and 21 is given for either anxiety or depression. Higher scores on each individual scale reflect severe forms of depression and/or anxiety. In the original study, Zigmond and Snaith have recommended a cut-off score of 7 for either subscale to be regarded as being in normal range, score of 8–10 being suggestive of the presence of respective mood disorder and a score of 11 or higher indicating the probable presence of mood disorder [21].

Sleep-related symptoms were assessed using validated questionnaires including Pittsburgh Sleep Quality Index (PSQI), and questions inquiring about specific disorders including sleep apnea and restless legs syndrome. PSQI is a validated questionnaire, which assesses seven elements of sleep quality: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleep medicine usage and daytime function. The total score is 21 points, with score of >5 indicating poor overall sleep quality [22]. OSA symptoms were assessed using two questions (loud snoring and long pauses between breaths while asleep). The presence of restless legs syndrome was assessed using four questions, i.e. the presence of unpleasant sensations in legs combined with urge or need to move the legs, frequency, feeling occurring mainly or only at rest and improvement with movement and if these feelings are worse in the evening or night than in the morning.

Spirometric measurement was done and GOLD class was assigned. Self-reported medication use and co-morbid medical condition were collected.

Statistics

SPSS software (version 22.0; SPSS, Chicago, IL) was used for the statistical analysis. Continuous variables were expressed as means ± SD. Difference between groups was assessed using ANOVA or Kruskal–Wallis test depending upon distribution of the data. Proportions were compared between groups using the chi-square test. Based on the PSQI score, the COPD groups were categorized into good (PSQI ≤ 5) and poor sleepers (PSQI >5). Correlations between health-related QoL, sleep quality and other variables were analyzed using non-parametric Spearman's correlation.

Multivariable logistic regression analysis was used to investigate relationship between sleep quality as the dependent variable and other independent variables. Variables selected for analyses were based on factors that have been identified in prior studies, spearman analysis and differences in characteristics observed between COPD patients classified as poor and good sleepers. Some of the prior studies have addressed factors such as severity of airflow obstruction, use of inhaled medications, tobacco status and psychiatric co-morbidities such as depression and anxiety [10, 23].

A p value of less than 0.05 was considered statistically significant.

Results

Of the 1123 subjects, 263 were healthy controls, 323 were smokers without COPD, and 537 had COPD (297 had mild, and 240 had moderate to severe disease); see Table 1 for subject characteristics. Patients with moderate-severe COPD had a significantly greater prevalence of cardiovascular co-morbidities including hypertension (44.6%), myocardial infarction (6.7%), peripheral artery disease (3.8%) and other medical co-morbidities such as sleep apnea (11.7%), depression (18.8%) and type 2 diabetes (13.3%). There was no significant difference between reported BiPAP and CPAP use between the groups.

Sleep quality, sleep disorders and nocturnal symptoms

PSQI total score was not significantly different between COPD and control groups; the mean baseline total PSQI scores were 5.0, 4.8, 5.0 and 5.1 in GOLD 1, GOLD 2+, and healthy and at-risk control subjects, respectively (Table 1). Overall, 36% of cohort reported poor sleep quality (PSQI >5).

Among COPD participants, 10.5% reported sleep latency >30 min, 12.3% reported sleeping ≤ 6 h, 10.3% took sleep aids three or more times a week, and sleep efficiency was $<85\%$ in 35.6%. Assessment of specific components of PSQI scores demonstrated that sleep disturbance had higher mean score relative to other components for both COPD and non-COPD control subjects (Table 2). Table 3 displays distribution of symptoms that caused sleep disturbances in COPD and non-COPD participants. The most common sleep disturbances in the COPD cohort, though not significantly different between groups, were "waking up in the middle of the night or early morning" (38.1%), "have to get up to use the bathroom" (56.2%) and "cannot sleep within 30 min" (11.4%). A greater percentage of patients with COPD participants reported, "have to get up to use the bathroom" as a factor that resulted in sleep disturbance compared to non-COPD subjects, which was statistically significant. Among COPD patients, a significantly greater percentage of patients with severe COPD reported breathing discomfort (11.1%) as a factor that resulted in sleep disturbance compared to mild and moderate COPD patients (1.0% and 2.4%, respectively) (Table 4).

Examining other plausible causes of sleep disruption, 8.4% of COPD patients reported a previous diagnosis of sleep apnea. 52% of COPD participants were able to answer the last part of the PSQI questionnaire involving a bed partner or roommate. Among the COPD responders ($n = 282$), approximately 49.2% reported loud snoring, and 10.8% stated witnessed apnea. Nonetheless, these variables were not significantly different in comparison to non-COPD healthy and at-risk control subjects, where the reported

Table 1. Baseline characteristics of CanCOLD cohort.

	Healthy	At-risk	GOLD1	GOLD2+	*p* value
Number of subjects	263	323	297	240	
PSQI global index	5.0 ± 3.3	5.1 ± 3.6	5.0 ± 3.5	4.8 ± 3.3	0.903
Poor sleeper (%)	36.3%	36.1%	37.4%	34.2%	0.898
Age (years)	66.7 ± 9.6	65.8 ± 9.5	68.4 ± 10.1	66.7 ± 10.2	**0.009**
Male (%)	46.8%	58.2%	71.0%	54.2%	**<0.001**
BMI (kg/m^2)	27.4 ± 5.0	28.4 ± 5.5	27.2 ± 4.5	28.3 ± 6.3	**0.011**
Waist circumference (cm)	96.0 ± 13.2	99.3 ± 14.1	97.8 ± 12.3	100.6 ± 15.3	**0.001**
Post-bronchodilator FEV_1 (L)	2.7 ± 0.8	2.8 ± 0.7	2.8 ± 0.7	1.8 ± 0.6	**<0.001**
Post-bronchodilator FEV_1/FVC (%)	77.7 ± 4.6	77.0 ± 4.7	64.3 ± 4.7	57.4 ± 9.8	**<0.001**
DLCO (% predicted)	110.0 ± 24.4	108.9 ± 23.8	108.6 ± 23.4	91.7 ± 25.3	**<0.001**
SF-36 MCS	51.1 ± 8.9	50.8 ± 9.3[a]	49.9 ± 9.3	49.9 ± 9.7	0.136
SF-36 PCS	52.3 ± 7.8	50.1 ± 9.6[a]	52.98 ± 7.7	47.5 ± 9.6	**<0.001**
HADS anxiety score	3.8 ± 3.1	3.9 ± 3.2[b]	3.6 ± 3.0	3.8 ± 2.9	0.759
HADS depression score	2.6 ± 2.6	2.8 ± 2.8[a]	2.6 ± 2.3	3.1 ± 2.5	**0.009**
Medical co-morbidities					
Coronary artery disease, *n* (%)	26 (9.9%)	36 (11.1%)	24 (8.1%)	17 (7.1%)	0.974
Hypertension	100 (38.0%)	**111 (34.4%)***	**99 (33.3%)***	**107 (44.6%)***	**0.034***
Myocardial infarction	8 (3.0%)	17 (5.3%)	**5 (1.7%)***	**16 (6.7%)***	**0.016***
Unstable angina	4 (1.5%)	9 (2.8%)	2 (0.7%)	7 (2.9%)	0.164
Stable angina	9 (3.4%)	8 (2.5%)	5 (1.7%)	10 (4.2%)	0.329
Heart failure	2 (0.8%)	2 (0.6%)	3 (1.0%)	7 (2.9%)	0.068
Peripheral artery disease	**2 (0.8%)***	4 (1.2%)	4 (1.3%)	**9 (3.8%)***	**0.044***
Valvular heart disease	**7 (2.7%)***	**1 (0.3%)***	2 (0.7%)	5 (2.1%)	**0.044***
Arrhythmia	32 (12.2%)	28 (8.7%)	32 (10.8%)	30 (12.5%)	0.434
Endocrine disorders					
Diabetes type 1	3 (1.1%)	3 (0.9%)	0	2 (0.8%)	0.38
Diabetes type 2	19 (7.2%)	38 (11.8%)	**21 (7.1%)***	**32 (13.3%)***	**0.026***
Psychiatric disorders					
Anxiety	23 (8.7%)	27 (8.4%)	15 (5.1%)	14 (5.8%)	0.225
Depression	**24 (9.1%)***	39 (12.1%)	40 (13.5%)	**45 (18.8%)***	**0.014***
Neurologic disorders					
Any cerebrovascular disease, *n* (%) including stroke and transient ischemic attack	9 (3.4%)	13 (4.0%)	19 (6.4%)	14 (5.8%)	0.303
Any neurologic disease, *n* (%) including dementia, Alzheimer's disease, MS, Parkinson's disease, ALS, other neurologic condition	25 (9.5%)	27 (8.4%)	18 (6.1%)	17 (7.1%)	0.451
Any musculoskeletal conditions, *n* (%)	129 (49.0%)	167 (51.7%)	154 (51.9%)	130 (54.2%)	0.72
Sleep apnea	18 (6.8%)	35 (10.8%)	**17 (5.7%)***	**28 (11.7%)***	**0.03***
CPAP use, *n* (%)	12 (4.6%)	16 (5.0%)	9 (3.0%)	16 (6.8%)	0.256
BiPAP use, *n* (%)	2 (0.8%)	2 (0.6%)	0	3 (1.3%)	0.286

*Between-group statistically significant difference.
[a]Sample size = 322.
[b]Sample size = 321.

Table 2. Individual sleep component scores in COPD patients in CanCOLD cohort.

Individual PSQI components	COPD	Non-COPD controls
Sleep quality	0.82 ± 0.73	0.86 ± 0.73
Sleep latency	0.88 ± 0.93	0.9 ± 0.96
Sleep duration	0.44 ± 0.79	0.46 ± 0.78
Sleep efficiency	0.62 ± 0.96	0.63 ± 0.94
Sleep disturbances	1.13 ± 0.51	1.12 ± 0.49
Use of sleep medicine	0.46 ± 0.98	0.47 ± 1.01
Daytime dysfunction	0.57 ± 0.63	0.65 ± 0.67

frequencies of previous diagnosis of sleep apnea, loud snoring and apnea were 9.0%, 49.5% and 9.8%, respectively. In addition, 16.0% of individuals in both non-COPD and COPD groups indicated being bothered by restless legs symptoms that occurred more than once a month.

Sleep quality and quality of life

SF-36 was used as a measure of overall health status. In CanCOLD cohort, there was a statistically significant difference in SF-36 PCS scores between groups, with lower scores observed in GOLD2+ in comparison to other groups. Among COPD participants, there was a significant difference in SF-36 PCS score between mild COPD and moderate to severe COPD patients with lower scores reported in latter the category (52.9 and 47.5, respectively, *p* value <0.001).

Table 3. The distribution of nocturnal symptoms among COPD and non-COPD participants.

Symptoms experienced three or more times in a week, *n* (%)	COPD *N* = 536	Non-COPD controls *N* = 586	*p* value
Cannot sleep within 30 min	61 (11.4%)	76 (13%)	0.42
Wake up in the middle of the night or early morning	204 (38.1%)	215 (36.7%)	0.64
Have to get up to use the bathroom	301 (56.2%)	277 (47.3%)	**0.003***
Cannot breathe comfortably	11 (2.1%)	13 (2.2%)	0.85
Cough or snore loudly	25 (4.7%)	28 (4.8%)	0.93
Feel too cold	10 (1.9%)	14 (2.4%)	0.55
Feel too hot	43 (8.0%)	43 (7.3%)	0.67
Bad dreams	9 (1.7%)	9 (1.5%)	0.85
Have pain	51 (9.5%)	57 (9.7%)	0.90

*$p < 0.05$; chi-square test.

Table 4. The distribution of nocturnal symptoms among patients with COPD.

Symptoms experienced three or more times in a week, *n* (%)	GOLD 1 *N* = 297	GOLD2 *N* = 212	GOLD 3+ *N* = 27	*p* value
Cannot get sleep within 30 min	36 (12.1%)	19 (9.0%)	6.0 (22.2%)	0.103
Wake up in the middle of night or early morning	122 (41.1%)	72 (34.0%)	10 (37.0%)	0.263
Have to get up to use the bathroom	174 (58.6%)	109 (51.4%)	18 (66.7%)	0.145
Cannot breathe comfortably	3 (1.0%)	5 (2.4%)	3 (11.1%)	**0.002***
Cough or snore loudly	14 (4.7%)	10 (4.7%)	1 (3.7%)	0.971
Feel too cold	7 (2.4%)	3 (1.4%)	0	0.566
Feel too hot	22 (7.4%)	20 (9.4%)	1 (3.7%)	0.495
Bad dreams	6 (2.0%)	3 (1.4%)	0	0.684
Have pain	24 (8.1%)	24 (11.3%)	3 (11.1%)	0.451

*$p < 0.05$; chi-square test.

Table 5. Baseline characteristics of good and poor sleepers among COPD and non-COPD patients.

	COPD			Non-COPD controls		
	Good sleeper (PSQI $\leq$ 5)	Poor sleeper (PSQI $>$ 5)	*p* value	Good sleeper (PSQI $\leq$ 5)	Poor sleeper (PSQI $>$ 5)	*p* value
Number of subjects (%)	341 (63.5%)	193 (36%)		371 (63.6%)	212 (36.4%)	
PSQI global index	2.8 ± 1.5	8.6 ± 2.5	**<0.001**	2.93 ± 1.36	8.80 ± 2.76	**<0.001**
Baseline characteristics						
Age (years)	67.3 ± 9.9	68.4 ± 10.6	0.229	66.3 ± 9.27	66.1 ± 9.99	0.772
Male (%)	240 (70.2%)	99 (51.6%)	**<0.001**	208 (56.1%)	102 (48.1%)	0.064
BMI (kg/m^2)	27.7 ± 4.9	27.6 ± 6.3	0.853	27.87 ± 5.27	28.10 ± 5.3	0.612
Waist circumference (cm)	99.9 ± 13.2	97.2.± 14.6	**0.03**	97.65 ± 13.43	98.0 ± 14.5	0.77
Post-bronchodilator FEV_1 (L)	2.45 ± 0.82	2.21 ± 0.78	**0.001**	2.82 ± 0.76	2.66 ± 0.7	**0.016**
Post-bronchodilator FEV_1/FVC (%)	61.3 ± 8.2	61.1 ± 8.3	0.854	77.28 ± 4.74	77.34 ± 4.6	0.874
DLCO (% predicted)	104.2 ± 26.5	95.6 ± 23.2	**<0.001**	110.79 ± 24.51	107.29 ± 23.1	0.107
Smoking history (pack-years)	21.7 ± 24.0	23.7 ± 26.6	0.363	9.28 ± 16.90	11.85 ± 25.0	0.184
Pulmonary inhaled medications						
Any MA	32 (9.4%)	19 (9.8%)	0.88	3 (0.8%)	2 (0.9%)	>0.999
Any BA	80 (23.5%)	52 (26.9%)	0.4	14 (3.8%)	21 (9.9%)	**0.003**
Any ICS	87 (25.5%)	56 (29.0%)	0.42	24 (6.5%)	31 (14.6%)	**0.001**
Symptoms and quality of life						
SF-36 – physical component	51.9 ± 8.2	48.3 ± 9.8	**<0.001**	52.43 ± 7.82	48.76 ± 10.1	**<0.001**
SF-36 – mental component	51.8 ± 8.0	46.6 ± 10.9	**<0.001**	52.86 ± 7.82	47.68 ± 10.6	**<0.001**
HADS anxiety score	3.0 ± 2.5	4.8 ± 3.3	**<0.001**	3.03 ± 2.43	5.19 ± 3.8	**<0.001**
HADS depression score	2.3 ± 2.2	3.6 ± 2.6	**<0.001**	2.01 ± 1.97	3.80 ± 3.4	**<0.001**
Symptoms suspicious of OSA, *n* (%)[a]	64 (30.9%)	32 (43.8%)	**0.046**	66 (28.1%)	44 (36.1%)	0.121
BiPAP use, *n* (%)	0	0	–	2 (0.5%)	2 (0.9%)	0.622
CPAP use, *n* (%)	17 (5.0%)	8 (4.2%)	0.672	16 (4.3%)	12 (5.8%)	0.446
Symptoms suspicious of RLS, *n* (%)[b]	40 (11.7%)	46 (24.0%)	**<0.001**	45 (12.2%)	46 (21.7%)	**0.003**
Self-reported sleep efficiency (%)	93.1 ± 7.5	75.4 ± 14.4	**<0.001**	92.37 ± 7.80	76.29 ± 14.8	**<0.001**

[a]Loud snoring, long pauses between breaths while asleep.
[b]The presence of unpleasant sensations in legs combined with an urge or need to move the legs, frequency, feeling occurring mainly or only at rest and improvement with movement, feelings are worse in the evening or night than in morning.

There was no significant difference in SF-36 MCS scores between the groups (Table 1).

HADS anxiety and depression scores were used to measure symptoms of depression and anxiety among individuals in CanCOLD cohort. In CanCOLD cohort, mean anxiety and depression scores were below 7 for all groups and there was no significant difference between groups for anxiety scale (Table 1).

Association of COPD and correlates of sleep quality

Table 5 compares the clinical characteristics among COPD and non-COPD subjects who were good and poor sleepers. Participants were categorized as good and poor sleepers based on global PSQI index. Good sleepers were individuals with PSQI $\leq$ 5 and poor sleepers were participants with PSQI $>$ 5. In this cohort, there was significant difference in various measures

Table 6. Multivariable logistic regression analysis of poor sleepers (PSQI > 5) among COPD participants.

Predictor	Correlation coefficient	Odds ratio	95% CI	*p* value
DLCO (% predicted)	−0.009	0.99	0.98–0.99	**0.026**
Waist circumference	−0.015	0.99	0.97–1.00	**0.043**
Restless legs syndrome symptoms	0.90	2.46	1.53–3.95	**0.00**
Obstructive sleep apnea symptoms	0.52	1.69	1.12–2.53	**0.012**
HADS depression score	0.13	1.14	1.05–1.25	**0.003**
HADS anxiety score	0.17	1.19	1.10–1.28	**0.00**

Highlighted: $p < 0.05$.
Dependent variable: poor sleep quality.
Only factors significantly associated with poor sleep quality are shown in this table. Baseline model included variables such as age, sex, BMI, waist circumference, post-bronchodilator FEV_1, predicted DLCO, tobacco status, use of inhaled medications (any beta-agonist, antimuscarinic and inhaled corticosteroids), restless legs syndrome and OSA symptoms.

related to pulmonary function and QoL measures. Among COPD participants, poor sleepers had lower diffusion capacity than those classified as good sleepers (104.2% predicted vs. 95.6% predicted, $p < 0.001$). In both the groups, participants with poor sleep quality had higher HADS anxiety and depression scores ($p < 0.001$), and lower SF-36 MCS and PCS than subjects classified as good sleepers ($p < 0.001$). There is evidence of association of sleep quality with post-bronchodilator FEV_1 and the presence of restless legs syndrome symptoms in COPD and non-COPD control groups, with lower FEV_1 values and more frequent reports of restless legs symptoms in poor sleepers. In addition, among COPD cohort, the presence of OSA symptoms was associated with worse sleep quality ($p = 0.046$). However, there was no reported association between use of BiPAP or CPAP with sleep quality in COPD and non-COPD groups. Use of inhaled pulmonary medications did not demonstrate association with sleep quality in COPD group ($p > 0.05$).

To assess independent associations with poor sleep quality (global PSQI > 5), multivariable logistic regression model was done (Table 6). Results presented in Table 6 are from a single model. Independent variables selected for analysis included factors such as age, sex, BMI, waist circumference, post-bronchodilator FEV_1, percentage predicted diffusion capacity, HADS anxiety and depression scores, restless legs and OSA symptoms, tobacco status (never-smokers, ex-smokers, current smokers) and use of inhaled medications (any muscarinic antagonist, beta-agonist, inhaled corticosteroids) (Table 7).

Among COPD participants, diffusion capacity (DLCO), restless legs symptoms, OSA symptoms, waist circumference and HADS anxiety and depression scores were identified as significant and independent predictors of poor sleep quality. Percentage predicted diffusion capacity and waist circumference showed negative association with poor sleep quality with odds ratio of 0.99, respectively. Patients with OSA and restless legs symptoms were more likely to have poor sleep quality with odds ratios of 1.69 and 2.46, respectively compared to those without symptoms. HADS anxiety and depression scores showed positive association with poor sleep quality with odds ratio of 1.19 and 1.14, respectively. Post-bronchodilator FEV_1, smoking status and use of inhaled medications were not significant predictors of poor sleep quality.

Table 7. Spearman correlation analysis among COPD patients.

Patient characteristics	PSQI global index
Sex	**0.149**
Age (years)	−0.006
BMI (kg/m^2)	−0.025
Waist circumference (cm)	−0.061
HADS anxiety score	**0.335**
HADS depression score	**0.332**
Post-bronchodilator FEV_1 (L)	**−0.107**
DLCO (% predicted)	**−0.154**
Tobacco status	0.036
OSA symptoms	0.065
RLS symptoms	**0.182**
Use of any beta-agonist	0.027
Use of any antimuscarinic	0.017
Use of any inhaled corticosteriods	0.048

Highlighted: $p < 0.05$.

Discussion

In our study, 36% of COPD patients were categorized as poor sleepers based on PSQI global index >5. This finding is in contrast to previous reports that have reported a higher prevalence of poor sleep quality (60%–70%) in patients with COPD [8, 24]. PSQI was not statistically different between COPD and control groups. In comparison to previous reports of COPD patients, the mean PSQI was lower in our COPD cohort; the mean PSQI scores of GOLD 1 and GOLD 2+ COPD subjects were 5.0 and 4.8, respectively, as opposed to scores higher than 6 found in previous studies [10, 14, 25]. These differences between studies may be because our subjects were drawn from the community rather than from the hospital or a specialist cohort and a greater proportion of our subjects had mild COPD [10, 14, 25]. In addition, patients were classified as COPD on basis of post-bronchodilator FEV_1/FVC ratio <0.70. This may have led to overestimation of COPD participants, as the GOLD criteria are prone to overdiagnosis of disease in close to 30% of older subjects [26]. It is possible that inclusion of non-COPD subjects by utilizing GOLD criteria to indicate disease may have led to lower prevalence of poor sleep quality in CanCOLD COPD cohort in comparison to previous studies. This is further reflected in our data showcasing comparisons between COPD and Non-COPD control subjects, which revealed several similarities among the groups.

First, in both the groups, similar associations were drawn between sleep quality- and health-related QoL measures and the presence of restless legs syndrome symptoms. Second, pulmonary function parameters including post-bronchodilator FEV_1 were shown to be associated with sleep quality, with lower measurements in poor sleep quality groups. Lastly, examination of individual components of PSQI index

revealed higher mean score for sleep disturbance relative to other components. With an exception of "Have to get up to use the bathroom" which was more frequently reported in COPD cohort, there was no significant difference with other nocturnal symptoms.

Percentage predicted DLCO was an independent predictor of poor sleep quality. Additionally, COPD patients classified as poor sleepers also had significantly lower predicted DLCO and post-bronchodilator FEV_1 than good sleepers. HADS anxiety score and depression score, waist circumference, symptoms of restless legs and OSA symptoms, were other variables identified as significant predictors of poor sleep quality in COPD patients.

There have been prior studies that have examined the association between COPD severity and sleep quality; however, large studies have not shown a consistent relationship between COPD severity and sleep disturbance. For instance, Omachi and coworkers showed that higher COPD severity score was associated with greater likelihood of sleep disturbance [9]. Contrary to these findings, another study highlighted that among COPD patients with airflow obstruction, a higher FEV_1 was associated with greater sleep disturbance. In our COPD subjects, when accounting for other variables in multivariable regression analysis, post-bronchodilator FEV_1 was not identified as an independent predictor of poor sleep.

A number of factors may contribute to poor sleep quality in COPD such as higher burden of respiratory symptoms, smoking status and concomitant medical co-morbidities. Our study demonstrated that a significantly greater proportion of severe COPD patients reported, "cannot breathe comfortably" as one of the complaints resulting in sleep disturbance. Other commonly reported complaints in COPD cohort, albeit not statistically significant included "waking up in the middle of the night or early morning" and "have to get up to use the bathroom".

We also observed a higher prevalence of cardiac co-morbidities including myocardial infarction, peripheral artery disease and hypertension in the moderate-severe COPD cohort. Other cardiovascular co-morbidities such as heart failure and arrhythmia were also present in greater proportion in moderate-severe COPD group, though not statistically significant in comparison to other groups. Prior work has recognized reduced lung function as an independent correlate of increased risk of heart failure, coronary artery disease and atrial fibrillation [27–29] and additionally, there is increased prevalence of insomnia in patients with cardiovascular disease [30]. Taken together, it is possible that the presence of these co-morbidities could be partially mediating sleep disturbances in COPD cohort.

Other factors such as inhalers used for management of COPD and smoking have also been suggested to impact sleep quality. In our study use of anticholinergic, beta-agonist or inhaled corticosteroids did not impact odds of poor sleep quality in COPD cohort. This finding is not surprising; as existing studies offer mixed results on effect of inhaler therapy on sleep quality [12, 31, 32]. More consistency is appreciated among studies that have examined association between smoking and sleep disturbance. Acute nicotine withdrawal during sleep and resultant sympathetic activation is one possible explanation offered for the negative affect of smoking on sleep quality [31, 33]. Contrary to earlier reports, in our study smoking status was not one of the independent predictors of poor sleep.

This work also highlights associations between depression, anxiety, and quality of measures and sleep quality. Poor sleep in COPD subjects was associated with worse indices of health-related QoL as indicated by SF-36 PCS and SF-36 MCS scores and less favorable HADS anxiety and depression scores. HADS anxiety score was also one of the predictors of poor sleep quality. Of note anxiety and depression have been known to share a bidirectional relationship with sleep dysregulation [34]. Similar association was noted between poor sleep quality and the presence of restless legs and OSA symptoms. Both of these variables were independent predictors of poor sleep quality in COPD participants. Many studies have reported sleep disturbance as one of the key consequences of restless legs syndrome [35, 36]. Patients with restless legs, experience irresistible urge to move their legs during periods of rest or inactivity, which tends to be worse during evening or night time hours. Due to nocturnal appearance of the symptoms, patients commonly report trouble with initiation of sleep, frequent nocturnal awakening and reduced sleep duration [35, 36].

Recognizing variables that impact sleep in COPD patients affords clinicians an opportunity to provide targeted therapy. Interventions directed towards these co-morbidities could improve sleep quality and vice versa. The presence of sleep problems is important to identify in COPD patients, as sleep disturbances can negatively impact QoL in COPD patients and are predictors of worse clinical outcomes [9].

This study has a number of limitations. First, sleep quality was based on subjective self-report questionnaire and no objective assessment such as in-lab polysomnography or actigraphy was conducted. Nonetheless, we view subjective reports as robust in an era of patient-centered outcomes. Second, our assessment about the presence or absence of OSA was based on self-report rather than physiological testing. As such we are likely under-reporting the presence of sleep-disordered breathing and its impact on sleep quality. In addition, among patients who reported BiPAP or CPAP use, we did not have compliance data to verify adequate usage. Next, our assessment about restless legs syndrome was based on questions regarding symptoms suggestive of restless legs syndrome, rather than validated questionnaire. Finally, this was a cross-sectional study; rather than a prospective longitudinal analysis making it difficult to make firm conclusions about causation. For example, anxiety or depression could cause poor sleep or vice versa. Despite these limitations, we believe our findings represent an important addition to the literature and hope that they encourage further research in this area.

Conclusions

In conclusion, total PSQI did not differ significantly between groups; however, patients with severe COPD have a high

prevalence of nocturnal breathing-related symptoms. COPD severity as defined by post-bronchodilator FEV_1 was not an independent predictor of poor sleep quality. Variables that were demonstrated to be predictors of poor sleep quality included predicted, DLCO, waist circumference, symptoms suggestive of restless legs syndrome and OSA and HADS anxiety and depression scores. Sleep disturbances can lead to adverse outcomes in COPD patients including increased frequency of COPD exacerbations and emergency health care utilization. Treatment directed towards recognized cofactors could help improve sleep dysregulation and thereby improve COPD-related outcomes.

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Declaration of interest

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